Bisphenol A and Infant Neonatal Neurobehavior

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We read with interest the article "Case Report: High Prenatal Bisphenol A Exposure and Infant Neonatal Neurobehavior" by Sathyanarayana et al. (2011). In their article, the authors proposed a potential association between a single, exceedingly high concentration of urinary bisphenol A (BPA) measured at the beginning of the third trimester of pregnancy in a single case mother and a single abnormal neurological assessment conducted 4 months later in a single and apparently otherwise healthy infant at approximately 1 month of age. We have several comments and concerns about this article and its conclusions.

First, the urinary BPA results for the mother at the 16-week gestation test and just after birth were not abnormally elevated; the only elevated concentration was at the 26-week gestation test. Sathyanarayana et al. (2011) reported that the elevated BPA level was the highest of any reported in the peer-reviewed literature and that the bioanalytical laboratory repeated the analysis to confirm the result. The actual values detected in the repeated analysis were not provided in the article, precluding readers from independently concluding that the result was likely not spurious.

Second, Sathyanarayana et al. (2011) stated that at 26 weeks of gestation the majority of the BPA in the urine sample was conjugated, indicating that it had been metabolized and thus did not reflect external contamination. It should be noted that glucuronidated BPA is not biologically active. The authors did not propose a potential mechanism by which conjugated BPA may exert neurological effects.

Third, although the neurological assessment conducted on the infant at approximately 1 month of age was considered abnormal, neurological assessments at 14 hr after birth and annually at 1–5 years of age were within normal limits, suggesting a spurious event. Also, it is unclear whether "normal limits" refers to results at 1–5 years of age for children in the Health Outcomes and Measures of the Environment (HOME) Study from which this case study was generated (and with which the 1-month assessment results were compared) or to some other data set. If it is the latter, the authors would appear to have compared the child's assessment results with two different data sets and drawn different conclusions from them without indicating whether (and how) the data sets differ.

The preceding items and other statements in the article raise doubt about the plausibility of a link between the single high urinary BPA measurement and the single abnormal neurological assessment. For example, Sathyanarayana et al. (2011) did not know how long the child exhibited symptoms after the abnormal assessment was conducted. The authors did not indicate that any follow-up tests were performed to detect ailments that may have been the cause of the abnormal findings; they stated only that there was "no obvious etiology." The authors reported that they referred the mother to her primary physician, but the only information they provided regarding the results of the follow-up or when it occurred was that

> [The] abnormal findings were not noted by any other medical assessments performed by health care providers, including the primary medical doctor for the infant. (Sathyanarayana et al. 2011)

Most strikingly, the authors stated that

> Other infants within the HOME Study had abnormal neurologic examinations, but some of these mothers did not have elevated prenatal urinary BPA concentrations. These cases may have resulted from other etiologies of abnormal neurobehavior that have not yet been explored.

We argue that the case infant also may have had such etiologies that were not explored. Thus, it is unclear to us why Sathyanarayana et al. (2011) chose to conduct and report a case study on this single infant, other than the fact that the mother had an unusually high urinary BPA concentration at a single time point.

In conclusion, we feel that it is highly likely that the elevated third-trimester urinary BPA concentration had absolutely nothing to do with the single abnormal neurological assessment in the case infant. We do not consider this study to be "hypothesis generating" but rather to simply fan the flames of a topic that has received substantial media attention, much of which is overblown and not supported scientifically. We recommend that the authors consider reviewing the Bradford Hill criteria for establishing causality before suggesting and publishing possible cause-and-effect relationships based on a single case study.

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Bisphenol A and Infant Neonatal Neurobehavior: Sathyanarayana et al. Respond

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In their letter, Haighton et al. recommend that we review Bradford Hill guidelines for establishing causality. As noted in our article (Sathyanarayana et al. 2011), we did not try to establish cause and effect with this single case study and cautioned against doing so. In medical research, new syndromes or toxicants have often been identified by the report of unusual cases or exposures, even though it is not always apparent with the initial case report. Thus, we believe that it is important to highlight this and other unusual cases to identify potential causative agents of neurobehavioral abnormalities in childhood. This case study does not stand in isolation; there is a growing body of animal and human literature documenting the neurodevelopmental impacts of bisphenol A (BPA) exposure (Braun et al. 2009; National Toxicology Program, Center for the Evaluation of Risks to Human Reproduction 2008; Yolton et al. 2011).

Haighton et al. state that glucuronidated BPA does not appear to be biologically active in mammalian systems; however, glucuronidated BPA can be deconjugated by the placenta or transferred across the placenta, where it can be deconjugated by other fetal tissues (Ginsberg and Rice 2009; Nishikawa et al. 2010). Therefore, a developing fetus can be exposed to a biologically active substance. Also, more recent literature has noted that BPA may be metabolized into other biologically active agents through oxidative cleavage to create the estrogenically active metabolite 4-methyl-2,4-bis(4-hydroxyphenyl)pent-1-ene (MBP), which is reported to be 500 times more potent than BPA *in vivo* (Okuda et al. 2010).

The authors were unclear about how "normal limits" for neurobehavioral assessment are defined. In our study (Sathyanarayana et al. 2011), we administered a wide range of standardized tests

that include validated threshold values that can be used to identify children at risk for delayed development or clinically significant behavioral problems (Bayley 1993; Gioia et al. 2003; Wechsler 2002). The comparison of the case child to these values is valid because the distribution of scores for children in our study are comparable to those in nationally representative population-based samples used to validate these instruments. This is how these tools are used clinically to identify children who may have neurobehavioral abnormalities.

Finally, Haighton et al. state that other etiologies could be responsible for the abnormal exam at 1 month of age. We stated this exact same point very clearly in our case report (Sathyanarayana et al. 2011). Although these other etiologies may be important in infant and child neurodevelopment, they would be confounders only if they are associated with both BPA exposure and neurodevelopment (Hernan et al. 2002).

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An Integrated Approach to the Exposome

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The editorial by Lioy and Rappaport (2011) provides a timely addition to the discussion about the exposome and exposure science. We are encouraged by the recognition of the importance of combining measurements of personal exposure with measurements of biological markers of exposure. However, rather than focusing on two approaches (i.e., top-down vs. bottom-up), we advocate a fully integrated approach to measurement of the exposome.

There are currently serious limitations in measuring internal and external exposure. It may be feasible to measure biological markers in blood or other media periodically, but such measures are not without difficulties. Recent developments in omics technology are very promising, but many of these techniques have low reproducibility between laboratories, show high intraindividual variability, and are still expensive; in addition, uncertainties remain in biological interpretation of these markers (Vineis et al. 2009). It is still often impractical to prospectively measure personal inhalation, dermal, and ingestion exposure. Such information could be collected periodically, but the scientific effort would be great and the intrusion into the subjects' lives would probably be unacceptable. Increased research effort will undoubtedly help improve measurement of both internal and external exposure. However, other sources of information exist that could contribute to constructing the exposome.

We all routinely leave traces of our exposome in everyday electronic databases or databases that could be easily constructed. For example, the goods we purchase in a supermarket are often tracked by loyalty cards, which may provide a rich source of information on food consumption and the consumer products we use. Consumption of electricity and natural gas is increasingly being logged electronically by utility companies to assist billing. These data could be used to determine use of electrical items (informative about exposure to electric and magnetic fields) and activity patterns. It is relatively straightforward to track movements of individuals using mobile phones, and these data can be used, for example, to help estimate exposure to air pollutants.

Within the next few years we will see an explosion in availability of sensors for many environmental contaminants that will be relatively cheap and easy to use and that could provide a more or less continuous log of information that can be related to exposure. These include simple sensors in the homes of subjects that continuously record information on air temperature, airborne contaminants, and other environmental factors. These sensors may provide personal exposure data or could, in combination with activity patterns and behavior, be used to reconstruct exposure profiles.

The availability of data on use and activity patterns, as well as developments in sensor and omics technology, suggests that the dichotomy in top-down and bottom-up approaches may not be appropriate, as there are other strategies that could be used to determine the exposome. In addition, the terms "top-down" and "bottom-up" may be interpreted differently, with consequent confusion of terminology. Instead, we should aim to develop a concept of the exposome that takes into account all sources of available exposure information.

The key factor in developing an integrated approach will be the articulation of clear theoretical paradigms linking exposures with disease. All of the exposure and contextual data could be used to reconstruct the exposome of individuals in an epidemiological study using appropriate models to link the data to parameters of interest in the exposome. Data on internal and external exposures, data on personal behavior, and environmental information from sensors could be used to triangulate on the exposome.

This is an extremely exciting time in exposure science, and we believe that the coming years will provide a great opportunity to make a significant leap forward in understanding the relationship between environmental exposure and disease. Maximizing the opportunities provided by various developments requires a fully integrated approach to the exposome. This approach must be based on a clear theoretical framework that incorporates measurement and modeling of